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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,403	06/20/2005	Jose Manuel Francisco Ochoa	2099.0090000	3497

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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
04/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,403	OCHOA, JOSE MANUEL FRANCISCO	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the Office action, mailed 01/06/09, is withdrawn. This action is a non-final action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Status of the Claims

Claims 1, 4, 6, 8, and 11 are currently pending in this application and are the subject of the Office action.

REJECTIONS

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6, 8, and 11 are rejected under 103(a) as being unpatentable over Seymour (Seymour. Glyburide/Metformin HCL Clinical Review In: Diabetes Intervention: Achieving tight glycemic control through combination therapy. Managed Care (Special Supplement). 2001; 10(2):1-24, especially pages 11-16), in view of McCall (McCall. Clinical review of glimepiride. Expert Opinion on Pharmacotherapy. 2001;2(4):699-713).

Seymour teaches Glucovance is an oral medication that combines glyburide and metformin hydrochloride, which offer complementary mechanisms for achieving glycemic control in patients with Type 2 diabetes (page 11, first para.). Seymour discloses clinical study trial results wherein diabetic patients were administered placebo, glyburide 2.5 mg alone, metformin 500 mg alone, glyburide 1.25 mg plus metformin 250 mg, glyburide 2.5 mg plus metformin 500 mg (page 13, col. 1, last full para.). Seymour discloses **conversion guides** showing how to switch diabetic patients on a combination of, for example,

glyburide and metformin hydrochloride (Glucophage) tablets, and glimepiride (Amaryl) tablets and metformin hydrochloride (Glucophage) tablets to Glucovance (page 14). In particular, Seymour teaches Glucovance tablets containing a combination of 5 mg glyburide and 500 mg metformin hydrochloride (Glucophage; page 14). Seymour teaches that patients on metformin and glyburide-metformin (5 mg/500 mg) were titrated to up to 4 tablets/day (= 20 mg of glyburide and 2000 mg of metformin hydrochloride, which would be equivalent to 8 mg glimepiride and 2000 mg of metformin hydrochloride based on the conversion factors of Seymour; page 15, last para., Table 2). Seymour discloses that in order to avoid hypolgycemia, the starting dose of Glucovance should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken and that the daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose necessary to **achieve adequate control of blood glucose** (page 14, Table 1, including footnotes; and page 15, Table 2, including footnotes). Seymour discloses that the Seymour states that the fixed dose combination of glyburide-metformin hydrochloride offers attendant gains in **patient compliance** in patients who are switched from polytherapy to fixed dose Glucovance monotherapy (page 16, last para).

However, Seymour does not teach the instant claimed combinations comprising glimepiride and metformin hydrochloride, or the instant claimed weight ratio.

McCall state that glimepiride is a second generation sulfonylurea for treatment of Type 2 diabetes (abstract). McCall discloses that glimepiride 's antihyperglycemic efficacy is equal to other secretagogues such as glyburide (abstract; page 703, col. 1, introduction section). Mccall teach that glimepiride is approved for use as monotherapy and for combination therapy with metformin and with insulin (abstract). McCall teaches that the dose of glimepiride 1-8 mg daily as monotherapy (page 706, col. 2). McCall state that glimepiride has some reasonable comparative data suggesting benefit over glyburide (page 709, col. 2, 3rd para.; page 720, conclusion section). McCall states that choosing a drug such as glimepiride merits serious consideration because it offers convenience, dosing flexibility and relatively low expense while minimizing the common barrier to ideal control and the most common adverse effect of **secretagogues**, hypoglycemia (page 710, col. 2, last para. to page 711, col. 1, line 20). McCall state that glimepiride appears to have a **lower risk of hypoglycemia than glyburide** (page 703, col. 2, introduction section).

It would have been obvious to a person of skill in the art at the time the invention was made to substitute the glyburide component in Glucovance as taught by Seymour with glimepiride as taught by Mccall for its reduced hypoglycemic adverse effects in treating a patient with type 2 diabetes mellitus (page 709, col. 2, 3rd para.; page 710, col. 2, last para. to page 711, col. 1, line 20; page 720, conclusion section). One would have been motivated to do so because Mccall suggest that glimepiride offers certain benefits over other secretagogues such as convenience, dosing flexibility and relatively low

expense, while minimizing the common barrier to ideal control and the most common adverse effect of secretagogues, hypoglycemia (page 710, col. 2, last para. to page 711, col. 1, line 20) and glyburide as taught by Seymour et al. is also a secretagogue. Since McCall teach that glimepiride is approved for use as monotherapy in a dose of 1-8 mg daily, and also for combination therapy with metformin (abstract; page 706, col. 2), and Seymour suggest that patients on glimepiride and metformin hydrochloride wherein both drugs are administered as separate dosage forms may benefit from a fix dose tablet formulation comprising metformin hydrochloride and a secretagogue (i.e. glyburide; page 14), one would reasonably expect to successfully substitute the glyburide component in the fixed dose Glucovance tablet formulation comprising metformin hydrochloride 500 mg with a suitable therapeutic dose of glimepiride, for example, of 1 mg (= relative dose ratio of 1/500 of glimepiride and metformin hydrochloride) to arrive at applicant's claimed fixed weight ratio of glimepiride and metformin hydrochloride of "about 1/500" for use in the treatment of a patient with type 2 diabetes mellitus since Seymour suggest that secretagogue - metformin hydrochloride combinations oral tablets offer complementary mechanisms for achieving glycemic control in patients with Type 2 diabetes (page 11, first para.) and may provide gains in patient compliance (page 16, last para.), particularly patients who a require polytherapy with two separate hypoglycemic agents (page 16, last para) and McCall state that glimepiride appears to have a lower risk of hypoglycemia than glyburide (page 703, col. 2, introduction section). Besides, it is routine in the medical arts to combine drugs that are known to have the same

therapeutic utility and both metformin hydrochloride and glimepiride are known hypoglycemic drugs as evidenced by the teaching of Seymour and McCall. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069 (CCPPA 1980).

With respect to claim 1, Seymour teaches tablets comprising metformin hydrochloride in a fixed dose combination with a secretagogue (i.e. glyburide), wherein the weight ratio of the secretagogue (i.e. glyburide) to metformin hydrochloride is 5mg/500mg (page 14) and suggest that patients requiring 2 mg of glimepiride and metformin hydrochloride 1000 mg – 2000 mg per day should receive an equivalent dose of glyburide/metformin hydrochloride of 2.5 mg/500mg (= 1 tablet of Glucovance) twice a day, which should be titrated in increments of 5mg/500mg of glyburide/metformin hydrochloride (= 1 tablet of Glucovance i.e. different strength from the 2.5/500 mg tablet; page 14, Table 1). Hence, one would reasonably expect to successfully modify the weight ratio of the secretagogue (e.g. glimepiride)-metformin hydrochloride components in the tablets of Seymour to arrive at the instant claimed weight ratio amounts depending on the dose amount of each agent required to achieve normoglycemic levels in a patient with type 2 diabetes absent objective evidence to the contrary. Besides, McCall teaches glimepiride in a dose of 1- 8 mg and Seymour discloses regimens comprising glimepiride 2- 8 mg and metformin hydrochloride 1000-2000 mg per day (page 14, Table 1) and therefore one would expect to select any conventionally known dose amount of each component to formulate a fix dose combination tablet (e.g. 2 mg glimepiride and 1000 mg metformin

hydrochloride = 1/500 weight ration; or 4 mg glimepiride and 2000 mg metformin hydrochloride = 1/500 weight ratio). Since the prior art encompasses a fixed dose combination comprising glimepiride to metformin hydrochloride in a weight ratio of 1/500 and the instant claims require a fixed dose combination of glimepiride to metformin hydrochloride in a weight ratio of about 1/500, one would reasonably expect that the fixed dose combination of the identical instantly claimed components in the same weight ratio would exhibit the same therapeutic properties, including being "a synergistic combination."

Regarding the preamble of claim 1, Seymour teaches Glucovance tablets and tablets comprising active drugs (e.g. glimepiride and metformin hydrochloride) would reasonably be considered to be solid pharmaceutical compositions.

Regarding claim 4, Seymour teaches tablet formulations comprising metformin hydrochloride 500 mg (Glucophage) and glimepiride (Amaryl; see page 14, Table 1) and McCall teaches glimepiride in doses of 1 mg - 8 mg (page 706, col. 2). Further, tablet formulations are routinely formulated with inert components (e.g. binders) to facilitate the pharmaceutical formulation and therefore one would reasonably expect that the tablets encompassed by the prior art would also contain at least one excipient since excipients (e.g. binders) are routinely added to tablet formulations. Hence, it would have been within the scope of knowledge and skill of an artisan at the time the invention was made to add any suitable excipient to the formulation to render it pharmaceutically desirable absent objective evidence to the contrary.

Regarding claim 6, Seymour disclose metformin hydrochloride 1000 mg and glimepiride 2 mg (page 14, Table 1). The above discussion of the limitation "at least one excipient" in connection with claim 4 is incorporated by reference.

Regarding claim 8, the above discussion of claim 1 is incorporated by reference. Further, it would have been obvious to a person of skill in the art at the time the invention was made to administer the fixed dose combination of glimepiride and metformin hydrochloride having any suitable weight ratio, including applicant's claimed weight ratio amount to control blood glucose levels. One would have been motivated to do so because Seymour suggest that secretagogue - metformin hydrochloride combinations oral tablets offer complementary mechanisms for achieving glycemic control in patients with Type 2 diabetes (page 11, first para.) and may provide gains in patient compliance (page 16, last para.).

Regarding claim 11, Seymour discloses that the daily dose of a fixed dose combination comprising administering a secretagogue (e.g. glyburide) should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose necessary to achieve adequate control of blood glucose (page 14, footnotes) such that one would reasonably expect to manipulate the relative dose amounts of glimepiride and metformin hydrochloride of the tablet composition encompassed by the prior art, including arriving at applicant's claimed dose amounts, and administer said fixed dose amounts (e.g. glimepiride 2 mg and metformin hydrochloride 1000 mg) to a patient with type 2 diabetes to achieve adequate control of blood glucose in a patient in said patient based on the

conventionally known doses of each agent as taught by Seymour absent objective evidence to the contrary (pages 14-15, Tables 1-2).

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to applicant's arguments

Applicant's arguments with respect to the rejection under 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-

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16 April 2009
/C. R./ Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611